Rejection under the Doctrine of Obviousness-Type Double Patenting

Claims 46-49 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over **claims 1-6 of U.S. Patent No. 6,414,132** in view of Coulombe et al. (Gene vol. 46, pp 89-95, 1986).

The Examiner states that one of ordinary skill in the art would have applied Coulombe et al.'s teaching of murine expression of recombinant genes to the method claims 1-12 of U.S. Patent No. 6,414,132 in order to produce the recombinant protein to study the role of different structural features of a gene in regulation of expression; and that it would have been *prima facie* obvious to apply Coulombe et al.'s mammalian expression which was well known at the time the invention was made to the claimed method of substituting preferred codons in order to abundantly express mammalian proteins for analysis. The Examiner also states that the method of producing the synthetic gene would obviously result in the product claims 46-48 which are drawn to a synthetic gene with less preferred codons replaced by preferred codons; and that it would have been *prima facie* obvious that one of ordinary skill in the art would apply Coulombe et al.'s mammalian expression system to the method claims 1-12 of U.S. Patent No. 6,414,132 in order to produce the recombinant product for analysis, inevitably resulting in the claimed synthetic gene.

To the extend that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

Applicants believe that the subject matter of the currently pending claims was originally presented (not in *ipsis verbis*) in the parent application 07/858,747, and made subject to a restriction requirement. Applicants submit that under 35 U.S.C. §121 , the currently pending claims should not be rejected over the issued Pavlakis et al. patents.

In light of the arguments presented above, Applicants respectfully request that the rejection of claims 46-49 under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of U.S. Patent No. 6,414,132 in view of Coulombe et al. be withdrawn.

Claims 46-48 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over **claims 3-12 of U.S. Patent No. 6,291,664** in view of Coulombe et al. (Gene vol. 46, pp 89-95, 1986).

The Examiner states that one of ordinary skill in the art would have applied Coulombe et al.'s teaching of murine expression of recombinant genes to the method claims 3-12 [and 33] of U.S. Patent No. 6,291,664 in order to produce the recombinant env protein to study the role of different structural features of a gene in regulation of expression; and that it would have been *prima facie* obvious to apply Coulombe et al.'s mammalian expression which were well known at the time the invention was made to the claimed method of substituting preferred codons in order to abundantly express mammalian proteins for analysis. The Examiner further submits that as claims 3-12 [and 33] of U.S. Patent No. 6,291,664, which are drawn to the HIV env gene, represent a species of the genus claims 46-48 of the instant application which are drawn to any synthetic gene, the species would render the genus obvious.

To the extend that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

In light of the arguments presented above, Applicants respectfully request that the rejection of claims 46-48 under the judicially created doctrine of obviousness-type double patenting over claims 3-12 of U.S. Patent No. 6,291,664 in view of Coulombe et al. be withdrawn.

Claims 46-48 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over **claims 3-6 of U.S. Patent No. 5,965,726** in view of Coulombe et al. (Gene vol. 46, pp 89-95, 1986).

The Examiner asserts that the skilled artisan would have applied Coulombe et al.'s teaching of murine expression of recombinant genes to the method claims 3-6 of U.S. Patent No. 5,965,726 in order to produce the recombinant gag protein to study the role of different structural features of a gene in regulation of expression; and that it would have been *prima facie* obvious to apply Coulombe et al.'s mammalian

expression which were well known at the time the invention was made to the claimed method of substituting preferred codons in order to abundantly express mammalian proteins for analysis. The Examiner also asserts that claims 3-6 of U.S. Patent No. 5,965,726 represent a species of a HIV gag construct with silent substitution to produce a more preferred codon of the genus claims 46-49 of the instant claim which are drawn to any synthetic gene expressed in an eukaryotic cell with a less preferred codon replaced by a preferred codon; and that the species would render the genus obvious.

To the extend that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

In light of the arguments presented above, Applicants respectfully request that the rejection of claims 46-48 under the judicially created doctrine of obviousness-type double patenting over claims 3-6 of U.S. Patent No. 5,965,726 in view of Coulombe et al. be withdrawn.

Claims 46-48 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over **claims 1-10 of U.S. Patent No. 5,972,596** in view of Coulombe et al. (Gene vol. 46, pp 89-95, 1986).

The Examiner asserts that the skilled artisan would have applied Coulombe et al.'s teaching of murine expression of recombinant genes to the method claims 1-10 of U.S. Patent No. 5,972,596 in order to produce the recombinant gag protein to study the role of different structural features of a gene in regulation of expression; and that the species (i.e., HIV gag gene) would render the genus (i.e., any synthetic gene) obvious.

To the extend that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

In light of the arguments presented above, Applicants respectfully request that the rejection of claims 46-48 under the judicially created doctrine of obviousness-type double patenting over claims 1-10 of U.S. Patent No. 5,972,596 in view of Coulombe et al. be withdrawn.

Claims 46-49 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over **claims 1-9 of U.S. Patent No. 6,174,666** in view of Coulombe et al. (Gene vol. 46, pp 89-95, 1986).

The Examiner states that the skilled artisan would have applied Coulombe et al.'s teaching of murine expression of recombinant genes to the method claims 1-9 of U.S. Patent No. 6,174,666 in order to produce the recombinant protein to study the role of different structural features of a gene in regulation of expression; and that it would have been *prima facie* obvious to apply Coulombe et al.'s mammalian expression which were well known at the time the invention was made to the claimed method of substituting preferred codons in order to abundantly express mammalian proteins for analysis. The Examiner further states that the method of producing the synthetic gene would obviously result in the product claims 46-48 which are drawn to a synthetic gene with less preferred codons replaced by preferred codons.

To the extend that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

In light of the arguments presented above, Applicants respectfully request that the rejection of claims 46-49 under the judicially created doctrine of obviousness-type double patenting over claims 1-9 of U.S. Patent No. 6,174,666 in view of Coulombe et al. be withdrawn.

Rejection under 35 U.S.C. §102

Claims 46-49 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Clark et al. (U.S. Patent No. 4,959,455; September 25, 1990).

The Examiner states that Clark et al. teach a method of constructing a synthetic gene and synthetic gene of primate IL-3 into a vector by recombinant techniques; and that the synthetic gene encoding IL-3 is normally expressed in eukaryotic cells. The Examiner further states that Clark et al. teach replacing a less preferred codon for a more preferred codon in both bacterial and mammalian systems; and that they teach

insertion of a synthetic gene in a vector as well as transfection into COS for a mammalian cell expression system.

To the extend that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

Claims 46 and 49 have been amended to clarify that the rarely-used or less preferred codon contains an "inhibitory/instability region". On page 9, lines 16-35, the specification shows that the invention relates to methods of increasing the stability and/or utilization of a mRNA produced by a gene by mutating regulatory or inhibitory/instability sequences (INS) in the coding region of the gene which prevent or reduce expression; and to constructs that contain such mutated genes. Applicants explain on page 9, lines 24-34 in the specification that an inhibitory/instability sequence is a regulatory sequence that resides within a mRNA transcript and is either (1) responsible for rapid turnover of that mRNA or (2) responsible for underutilization of that mRNA or (3) both. On page 40, lines 14-21, Applicants state that the mutated mRNA can be analyzed and compared to the unmodified mRNA containing the inhibitory/instability region(s). As an example, HIV-1 p17gag mutants are compared to the unmutated HIV-1 p17gag in transfection experiments with subsequent analysis of the mRNAs by Northern blot analysis. It is clear from Applicants' disclosure that the invention is concerned with increasing the stability and utilization of mRNA produced by a gene. This is accomplished by mutating specific regions in the coding sequence of a gene, i.e., the inhibitory/instability regions. An example of such a mutation is a conservative or non-conservative amino acid substitution (see page 10, line 8) or multiple point mutations (see page 10, line 34 and page 20, lines 6-8) or altering less-preferred codons to more preferred codons (see page 20, lines 31-33).

In comparison, Clark et al. teach a family of primate IL-3 growth factors (see column 4, lines 60-61) and nucleotide modifications of IL-3 related sequences (see column 6, line 44). Specifically, Clark et al. indicate that examples of such modifications are IL-3 related sequences that include the replacement of one or both of the two cysteine residues in each coding sequence to eliminate disulfide bridges (see column 6, lines 56-

61); or modifications of the glycosylation sites (column 6, lines 66-67) which are normally recognized by glycosylation enzymes (column 7, lines 5-6), wherein amino acid substitutions or deletions result in non-glycosylation (see column 7, lines 8-12). Although, Clark et al. teach possible modifications of the IL-3 like factors, they do not disclose modification of any inhibitory/instability region(s). In fact, Clark et al. neither disclose inhibitory/instability region nor do they disclose or even suggest the mutating of inhibitory/instability regions in the coding sequence of a gene. Thus, Clark et al. do not anticipate the claimed invention.

As the Examiner is well aware of, for a rejection under 35 U.S.C. §102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. v. Union Oil Co. Of California,* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.,* 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference....There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features or limitations of the presently claimed invention.

The office action cites Clark et al. as the basis for the §102(b) rejection. Applicants respectfully submit that Clark et al. do not disclose every element of the presently claimed invention and, thus, the reference can not form the basis for a §102(b) rejection. Particularly, because the cited reference does neither expressly nor inherently disclose a synthetic gene encoding a protein wherein at least one rarely-used or less preferred codon containing an inhibitory/instability region has been replaced by a

preferred codon encoding the same amino acid. Similarly, the cited reference does neither expressly nor inherently disclose a method for preparing a synthetic gene encoding a protein, including identifying rarely-used and less-preferred codons containing an inhibitory/instability region and replacing one or more of said rarely-used or less-preferred codons with a preferred codon encoding the same amino acid as the replaced codon.

In light of the amendment and arguments presented above, Applicants respectfully request that the rejection of claims 46-49 under 35 U.S.C. §102(b) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 46 has been amended as follows:

46. (Amended) A synthetic gene encoding a protein normally expressed in an eukaryotic cell wherein at least one rarely-used or less preferred codon in a natural gene encoding said protein has been replaced by a preferred codon encoding the same amino acid, and wherein said rarely-used or less preferred codon contains an inhibitory/instability region, said synthetic gene expressing said protein at a level which is higher than that expressed by said natural gene in an in vitro mammalian cell culture system under identical conditions.

Claim 49 has been amended as follows:

49. (Amended) A method for preparing a synthetic gene encoding a protein normally expressed by mammalian cells, comprising identifying rarely-used and less-preferred codons containing an inhibitory/instability region in the natural gene encoding said protein and replacing one or more of said rarely-used or less-preferred codons with a preferred codon encoding the same amino acid as the replaced codon, so that a synthetic gene is prepared.

IN THE SPECIFICATION:

The reference to priority on page 1 has been amended as follows:

This application is a continuation of U.S. Serial No. 09/678,437, filed October 2, 2000, now U.S. Patent No. 6,414,132; which is a continuation of U.S. Serial No. 09/414,117, filed October 8, 1999, now U.S. Patent No. 6,291,664; which is a continuation of U.S. Serial No. 08/850,049, filed May 2, 1997, ~~(~~now U.S. Patent 5,965,726~~)~~; which is ~~in turn~~ a continuation of U.S. Serial No. 08/050,478, now U.S. Patent No. 5,972,596; which is a 371 of PCT/US93/02908, filed March 29, 1993; ~~of the National Stage under 35 U.S.C.~~

~~§371; of PCT/US93/02908 filed March 29, 1993;~~ which is ~~in turn~~ a continuation-in part of U.S. Serial No. 07/858,747, filed March 27, 1992, ~~(~~now U.S. Patent No. 6,174,666B1~~)~~. The disclosures of each of these applications is hereby incorporated by reference.

IN THE DRAWINGS:

The figure legend "Fig. 1" on the second sheet of Figure 1 (C) was amended as follows:

Fig. 1 continued

The figure legend "Fig. 14" on the second, third, and forth sheet of Figure 14 (B, C, and D, respectively) has been amended as follows:

Fig. 14 continued

The title of Figure 13 has been amended as follows:

POINT MUTATIONS ELIMINATING THE NEGATIVE EFFECTS OF CRS IN THE pol REGION (nucleotides 3700-4194) (SEQ ID NO: 127)

The following new title has been added to Figure 14B:

COMPLETE NUCLEOTIDE SEQUENCE OF p37M1-10D AND AMINO ACID SEQUENCE OF $p37^{gag}$ PROTEIN (SEQ ID NO: 129)